IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

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Applicant(s)	:	Borodic, Gary E.
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Examiner	:	Gerald R. Ewoldt
Docket No.	:	33677-00600US
Customer No.	:	000038647
Title	:	***Chemodenervating Pharmaceutical As Anti-Inflammatory Agent***

MAIL STOP APPEAL BRIEF – PATENTS
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APPEAL TO THE BOARD OF PATENT APPEALS AND INTERFERENCES UNDER 37 C.F.R. 41.37

In response to the Pre-Appeal Brief Review Panel decision dated May 22, 2006, Applicant respectfully submits the following Appeal Brief. A Notice of Appeal was filed on April 13, 2006, concurrently with the Pre-Appeal Brief Request For Review.

In view of the following arguments, Applicant respectfully requests reconsideration and allowance of the pending claims.

I. REAL PARTY IN INTEREST

The real parties in interest are Botulinum Toxin Research Associates, Inc., the assignee and Dr. Gary Borodic, the applicant.

II. RELATED APPEALS AND INTERFERENCES

There are no related Appeals or Interferences known to Appellants which will directly affect, be affected by, or have a bearing on the Board's decision in the instant appeal.

III. STATUS OF CLAIMS

Upon entry of the Amendment After Final submitted concurrently herewith, (canceling claims 17-19 and 21-23) claims 1, 5-8, 10-12, 24, 25 and 42-57 are pending and presently on appeal.

IV. STATUS OF AMENDMENTS

The Amendment and Response After Final filed on February 13, 2006 included a request that claims 17-19 and 21-23 be canceled, but the amendment was not entered because it was alleged that the "Applicant has submitted 33 pages of new arguments that would comprise further consideration." See Advisory Action mailed March 30, 2006 at Continuation of 3.

In order to simplify the issues on appeal, Applicant submits concurrently herewith a second Amendment After Final, with no argument, requesting that claims 17-19 and 21-23 be canceled. Entry of the Amendment is respectfully requested.

V. SUMMARY OF CLAIMED SUBJECT MATTER

Independent claim 1 (Claims Appendix at page 38) is directed to a method of reducing inflammation, comprising the step of administering a therapeutically effective dose of a botulinum toxin to an affected area of a subject suffering from inflammation, wherein the botulinum toxin reduces at least one symptom of inflammation, and wherein said therapeutically effective dose is sufficient to reduce said at least one symptom of inflammation but less than a dose necessary to produce substantial muscle weakness within the affected area. (See, for example, originally filed claim 2; page 19, lines 4-5; page 3, line 21 through page 4, line 2; and page 4, lines 8-11).

Independent claim 10 (Claims Appendix at 39) is directed to a method for treating allergic blepharoconjunctivitis comprising the step of administering a therapeutically effective dose of a botulinum toxin in a periocular area of a subject suffering from blepharoconjunctivitis, thereby reducing inflammation. (See, for example, originally filed claim 10; page 7, lines 13-15; page 15, lines 1-15; page 20, lines 6-19; Figure 6; and Figures 3-5).

Independent claim 11 (Claims Appendix at 39) is directed to a method for treating classic type 1 hypersensitivity comprising the step of administrating a botulinum toxin to an affected area of a subject suffering from classic type 1 hypersensitivity, thereby reducing inflammation. (See, for example, originally filed claim 11; page 5, lines 12-18; and page 20, lines 6-19).

Independent claim 24 (Claims Appendix at 39) is directed to a method for treating inflammation, comprising the step of administering a botulinum toxin to an affected area

of a subject suffering from inflammation in a therapeutically effective dose sufficient to reduce a rapid-phase inflammatory response under neural regulation, thereby reducing at least one symptom of inflammation, and wherein said therapeutically effective dose is sufficient to reduce the at least one symptom of inflammation but less than a dose necessary to produce substantial muscle weakness within said affected area. (See, for example, originally filed claims 1 and 2; page 7, lines 9-12; page 19, lines 4-5; page 3, line 21 through page 4, line 2; and page 4, lines 8-11).

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

1. Whether claims 1, 5-8, 24, 25, 42, 43 and 46-57 are unpatentable under 35 U.S.C. § 112, first paragraph, as being based on a nonenabling disclosure of "a method of reducing inflammation without causing muscle weakness."

2. Whether claims 10-12 are unpatentable under 35 U.S.C. § 103 over U.S. Pat. No. 6,063,768 in view of the Merck Manual.

3. Whether claims 1, 5-8, 10-12, 21-25 and 42-57 are unpatentable under 35 U.S.C. § 112, first paragraph, as being based on a disclosure lacking written description support for the claimed invention.

VII. ARGUMENT

A. The Rejection of Claims 1, 5-8, 24, 25, 42, 43 and 46-57 under 35 U.S.C. § 112 First Paragraph

Claims 1, 5-8, 24, 25, 42, 43 and 46-57 stand rejected under 35 U.S.C. § 112, first paragraph, because it is alleged that the specification does not enable a method of reducing inflammation without causing muscle weakness. Applicant respectfully traverses the rejection for at least the following reasons: (1) the Office has not met its burden of establishing a *prima facie* case of lack of enablement because four of the eight Wands factors have not been considered by the Office; (2) no experimentation would be required to practice the claimed invention and the Office bases its determination of lack of enablement on conclusory statements that ignore or discount what is taught in the specification; and (3) the Office has provided no evidence to support its position that the statements made in the specification should not be accepted. Applicant respectfully asserts that the rejection is therefore improper and should be withdrawn.

1. The Law Regarding Enablement

The analysis of whether a particular claim is supported by the disclosure in an application is discussed in detail in the MPEP at 2164.01 and 2164.01(a) *et seq*. Before the Office may assert that a claim is not supported by the disclosure in an application, it must conduct a detailed analysis. This analysis requires a determination of whether the disclosure, when filed, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention.

The enablement provision requires that the patentee provide a written description of the invention "in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same." 35 U.S.C. § 112, ¶ 1. The purpose of this requirement is to ensure that "the public knowledge is enriched by the patent specification to a degree at least commensurate with the scope of the claims." *Nat'l Recovery Techs., Inc. v. Magnetic Separation Sys., Inc.*, 166 F.3d 1190, 1195-96 (Fed. Cir. 1999); see also Donald S. Chisum, 3 Chisum on Patents § 7.01 (2002). Accordingly, the Federal Circuit has held that the specification must provide sufficient teaching such that one skilled in the art could make and use the full scope of the invention without undue experimentation. *CFMT, Inc. v. Yieldup Int'l Corp.*, 349 F.3d 1333, 1338 (Fed. Cir. 2003); *Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1365 (Fed. Cir. 1997); *In re Wands*, 858 F.2d 731, 736-37 (Fed. Cir. 1988). "The key word is 'undue,' not 'experimentation.'" *Wands*, 858 F.2d at 737. That is, the specification need only teach those aspects of the invention that one skilled in the art could not figure out without undue experimentation. See, e.g., *Nat'l Recovery Techs.*, 166 F.3d at 1196 ("The scope of enablement . . . is that which is disclosed in the specification plus the scope of what would be known to one of ordinary skill in the art without undue experimentation."); Wands, 858 F.2d at 736-37 ("Enablement is not precluded by the necessity for some experimentation such as routine screening."). Although the ultimate determination of whether one skilled in the art could make and use the claimed invention without undue experimentation is a legal one, it is based on underlying findings of fact. *CFMT*, 349 F.3d at 1337. Furthermore, "whether

undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." *Wands*, 858 F.2d at 737. Some of these considerations, commonly referred to as "the Wands factors," include "(1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims." Id.; *see also Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1213 (Fed. Cir. 1991)

Importantly, it is improper to conclude that a disclosure is not enabling based on an analysis of only one of the above factors while ignoring one or more of the others. The examiner's analysis must consider all the evidence related to each of these factors, and any conclusion of nonenablement must be based on the evidence as a whole. *In re Wands,* 858 F.2d at 737, 740, 8 USPQ2d at 1404, 1407. See also MPEP at 2164.01(a).

Thus, the determination that "undue experimentation" would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the above noted factual considerations. *In re Wands,* 858 F.2d at 737, 8 USPQ2d at 1404.

2. The Rejection for Lack of Enablement is Improper and Should be Withdrawn

In the instant case, the Office has not conducted the required analysis because it has not considered all of the facts and has ignored four of the eight Wands factors. A *prima facie* case of lack of enablement has therefore not been set forth by the Office. Applicant respectfully asserts that the Office bases its determination on conclusory

statements that ignore or discount what is taught in the specification without providing any reasons for doing so. Finally, the Office has provided no evidence to support the position that the statements made in the specification should not be accepted. Therefore, the determination that the rejected claims are not enabled by the disclosure is improper and should be withdrawn.

The basis for the enablement rejection seems to be that the Office does not accept affirmative statements made in the specification. The office asserts that the claimed method would involve "unpredictable factors." Specifically, the Office states that "the specification simply does not disclose that muscle weakness was ever measured." Final Office Action at page 3.

While the Office acknowledges that "reduced inflammation was noted" it discounts this observation by stating that it was "only as a side effect of treatment for other disorders." Final Office Action at page 3. The Office also states that "[a]ccordingly, claims drawn to reducing inflammation without causing muscle weakness, assertedly due to a new (and previously unknown) 'bioeffect', must be considered to be inherently unpredictable and requiring some sort of enablement in addition to mere assertion." Final Office Action at page 3.

In its discussion of the examples, the Office states that "[f]or none of these patients [in the examples] was it disclosed that the doses of Botox™ employed were sufficient to reduce inflammation but below that necessary to cause substantial muscle weakness. Indeed, in most of these cases it appears that Botox™ was employed in a

method intended to cause muscle weakness and an anti-inflammatory side effect was observed." Final Office Action at page 3.

a. The Wands Factors

As stated above, a *prima facie* case of lack of enablement has not been set forth by the Office.

1. Scope or Breadth of the Claims

The first Wands factor requires an analysis of whether or not the enablement provided by the specification is commensurate with the scope of the claims. Claim 1 of the application is representative and it recites:

> 1. A method of reducing inflammation, comprising the step of administering a therapeutically effective dose of a botulinum toxin to an affected area of a subject suffering from inflammation, wherein the botulinum toxin reduces at least one symptom of inflammation, and wherein said therapeutically effective dose is sufficient to reduce said at least one symptom of inflammation but less than a dose necessary to produce substantial muscle weakness within the affected area.

The Office alleges that "a method of reducing inflammation without causing muscle weakness" is not enabled by the specification. Applicant disagrees because the specification clearly provides enablement for the scope of this claim (as well as all of the claims).

For example, the specification teaches specific doses of botulinum toxin that can be used by a skilled artisan to practice "a method of reducing inflammation without causing muscle weakness." See page 19 of the specification. A skilled artisan would know how to prepare and administer doses of botulinum toxin to practice the invention

based on a simple reading of the specification. Any experimentation required to do this would be nothing more than routine. In particular:

- Original claim 2 recites "A method of treating inflammation, comprising the step of administering a chemodenervating agent to an anatomic region in a dose just sufficient to reduce inflammation, but below that necessary to cause substantial muscle weakness." Referring to the specification, as outlined below, the skilled artisan would know what these doses are.
- On page 19 of the specification, Applicant teaches that "Minimum doses range between 0.6 units to 15 units and are far lower than that required to produce regional weakness."
- On page 3 of the specification, in the Summary of the Invention, Applicant teaches that "It has been found that the use of botulinum toxin in doses from 1/3rd to several orders of magnitude less than those associated with treatment of regional movement diseases has been effective to reduce inflammation and adverse sensory experiences associated with the inflammation response."
- On page 4 of the specification, Applicant teaches that "It is a finding of the subject invention that chemodenervative pharmaceuticals such as botulinum toxin in low dosages are effective anti-inflammatory agents. Typical minimum effective doses range from 0.5-5 units as opposed to 20-600 units used for treatment of movement disorders."

Applicant respectfully asserts that the specification enables the scope of the claimed invention because it teaches how to practice "a method of reducing inflammation without causing muscle weakness." A skilled artisan reading the specification would be informed of the doses of botulinum toxin to use in the claimed methods and would be able to practice the full scope of the invention without undue experimentation.

2. The Nature of the Invention, State of the Prior Art and Level of One of Ordinary Skill

The second, third and fourth Wands factors require an analysis of whether the specification would have been enabling as of the filing date and involves consideration of the nature of the invention, the state of the prior art, and the level of skill in the art. See MPEP at 2164.05(a). There is no evidence that the Office has considered these three Wands factors. For this reason alone, Applicant respectfully asserts that no *prima facie* case of non enablement has been made because the Office has not met its burden of conducting the required analysis.

As stated in the MPEP at 2164.01(a): it is improper to conclude that a disclosure is not enabling based on an analysis of only one of the Wands factors while ignoring one or more of the others. The examiner's analysis must consider all the evidence related to each of these factors, and any conclusion of nonenablement must be based on the evidence as a whole. *In re Wands,* 858 F.2d at 737, 740, 8 USPQ2d at 1404, 1407. See MPEP at 2164.01(a). Applicant respectfully asserts that the rejection is improper and should be withdrawn.

3. The Level of Predictability in the Art and Amount of Direction Provided by the Inventor

The fifth and sixth Wands factors require an analysis of the amount of guidance or direction needed to enable the invention and is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. See MPEP at 2164.03. The Office Action concludes, without any analysis, that "claims drawn to reducing inflammation without causing muscle weakness, assertedly due to a new (and previously unknown) 'bioeffect', must be considered to be inherently unpredictable and requiring some sort of enablement in addition to mere assertion." No explanation is given to define what is meant by the term "inherently unpredictable" or why the instant claims fall into this category, newly created by the Office.

Applicant respectfully asserts that the claimed methods are not "inherently unpredictable" as alleged by the Office because more than sufficient guidance is provided in the specification to allow a person having ordinary skill in the art to practice the invention. For example, applicants teach observations in patients and approaches to disease treatment (pages 10-20), treatment of a series of patients with blepharoconjunctivitis (page 15) and treatment in an animal model (page 13). Applicants submit that this is hardly an unpredictable sequence of findings and indicates a high level of predictability.

The guidance provided for practicing the invention may be found throughout the specification. Some of these specific teachings are highlighted above under the discussion of the first Wands factor. The specification teaches the doses required to achieve the claimed effects. As stated in the MPEP at 2164.03, "If one skilled in the art

can readily anticipate the effect of a change within the subject matter to which the claimed invention pertains, then there is predictability in the art."

4. The Existence of Working Examples

The MPEP at 2164.02 clearly states that "Compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed." [emphasis added]. In spite of this, the Office continues to insist that "the specification simply does not disclose that muscle weakness was ever measured." Office Action at page 3.

In the instant case, even if it were true (which it is not) that no examples are disclosed in the specification, this would not constitute grounds for alleging a lack of enablement because examples are simply not required. Furthermore, the absence of examples is not dispositive of whether a claimed invention is enabled by the disclosure.

In any event, Applicants respectfully disagree with the allegation that no examples have been provided that support the claimed invention. Applicants point particularly to the example directed to spasmodic torticolis beginning on page 17 of the specification. The Office has provided no reason as to why the examples should be discounted or why they do not enable the claimed invention. Withdrawal of the rejection is respectfully requested.

5. The Quantity of Experimentation Needed to Make or Use the Invention Based on the Content of the Disclosure

The last of the Wands factors requires an analysis of the amount of experimentation needed to make or use the invention based on the content of the disclosure.

There is no evidence that the Office has considered this Wands factor in any of its rejections. For this reason alone, Applicant respectfully asserts that no *prima facie* case of non enablement has been made because the Office has not met its burden of conducting the required analysis. The Office has ignored this Wands factor as well as the three factors discussed above. This is improper.

Applicant respectfully asserts that no experimentation would be required to practice the claimed invention; and if any experimentation were required, it would be nothing more than routine. Applicant teaches the doses of botulinum toxin required to obtain the desired effects and a person having skill in the art could practice the invention by simply reading the disclosure and following its teachings.

For all of the foregoing reasons, Applicant respectfully asserts that the rejection is improper and should be withdrawn.

B. The Rejection of Claims 10-12 under 35 U.S.C. § 103(a)

The cited prior art references do not disclose or suggest all aspects of claims 10-12.[1] Applicant respectfully asserts that the Office has not provided sufficient evidence that one of ordinary skill in the art would have been motivated to combine the cited prior art references to arrive at the claimed invention. Thus, the Examiner has not established a *prima facie* case of obviousness of the pending claims. The rejection should therefore be reversed.

1. The Law Regarding Obviousness

Section 103 of Title 35 provides:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

35 U.S.C. § 103(a); *See also Graham v. John Deere Co.*, 383 U.S. 1, 14, 86 S. CT. 684 (1966); *In re Dembiczak*, 175 F.3d 994, 998 (Fed. Cir. 1999).

The determination of obviousness and, thus, patentability, is a question of law based on several underlying factual determinations: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed invention and the prior art; and (4) objective indicia of nonobviousness or secondary considerations. *See Sandt Technology, Ltd. v. Resco Metal and Plastics Corp.*, 264 F.3d

[1] Claims 17-19 and 21-23 are cancelled in the Amendment After Final submitted concurrently herewith.

1344, 1354 (Fed. Cir. 2001); *Rockwell Int'l Corp. v. United States*, 147 F.3d 1358, 1362 (Fed. Cir. 1998).

When obviousness is based on the teachings of multiple prior art references, the Examiner must also establish some clear "suggestion, teaching, or motivation" that would have led a person of ordinary skill in the art to combine the relevant prior art teachings in the manner claimed. *See Abbott Laboratories v. Andrx Pharmaceuticals, Inc.*, 452 F.3d 1331, 1336 (Fed. Cir 2006); *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1164 (Fed. Cir. 2006); *Tec Air, Inc. v. Denso Mfg. Mich. Inc.*, 192 F.3d 1353, 1359-60 (Fed. Cir. 1999); *Pro-Mold & Tool Co. v. Great Lakes Plastics, Inc.*, 75 F.3d 1568, 1572 (Fed. Cir. 1996). "It is insufficient to establish obviousness that the separate elements of the invention existed in the prior art, absent some teaching or suggestion, in the prior art, to combine the elements." *Kahn v. General Motors Corp.*, 135 F.3d 1472, 1480 (Fed. Cir. 1998). "[T]he record must provide a teaching, suggestion or reason to substitute [one element] for the system of [another element] in the prior art. The absence of such a suggestion to combine is dispositive in an obviousness determination." *Gambro Lundia AB v. Baxter Healthcare Corp.*, 110 F.3d 1573, 1578-79 (Fed. Cir. 1997).

The reason, suggestion, or motivation to combine prior art references "may be found explicitly or implicitly: (1) in the prior art references themselves; (2) in the knowledge of those of ordinary skill in the art that certain references, or disclosures in those references, are of special interest or importance in the field; or (3) from the nature of the problem to be solved, 'leading inventors to look to references relating to possible solutions to that problem.'" *Ruiz v. A.B. Chance Co.*, 234 F.3d 654, 665 (Fed. Cir. 2000)

(*quoting Pro-Mold*, 75 F.3d at 1572); s*ee also Medichem*, 437 F.3d at 1165. Federal Circuit case law "makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references." *Dembiczak*, 175 F.3d at 999. "Combining prior art references without evidence of such a suggestion, teaching, or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability—the essence of hindsight." *Dembiczak*, 175 F.3d at 999.

The Examiner must explain with particularity not only the requisite motivation of one of ordinary skill in the art to combine the prior art teachings, but also some motivation to combine the prior art teachings in the particular manner claimed. *See In re Kotzab*, 217 F.3d 1365, 1371 (Fed. Cir. 2000) ("Particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed."); *In re Rouffet*, 149 F.3d 1350, 1357 (Fed. Cir. 1998) ("In other words, the examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed.").

The obviousness determination must be evaluated "at the time the invention was made." 35 U.S.C. § 103(a); s*ee In re Raynes*, 7 F.3d 1037, 1039 (Fed. Cir. 1993) ("analytic focus is upon the state of knowledge at the time the invention was made. The Commissioner bears the burden of showing that such knowledge provide some teaching,

suggestion, or motivation to make the particular combination that was made by the applicant."). The emphasis on the time of the invention forces the decision-maker to avoid improper hindsight reconstruction employing the features of the claimed invention.

2. The References of Record do not Render the Claims Obvious

The rejection of the pending claims is erroneous for the reasons discussed below, including: (1) features of the rejected claims are not found in the prior art, as the Examiner admits; and (2) the Examiner did not provide sufficient evidence that one of ordinary skill in the art would have been motivated to combine the features of the '768 patent with the Merck Manual. As such, a *prima facie* case of obviousness has not been made. Given proper consideration, the conclusion that Appellant's claims are unpatentable must be withdrawn.

Claims 10-12 stand rejected under 35 U.S.C. § 103(a) for allegedly being unpatentable over U.S. Patent No. 6,063,768 ("the '768 patent") in view of the Merck Manual (1992).

In the Office Action mailed July 5, 2001, the Office acknowledges the following deficiencies in the '768 patent:

> The '768 patent differs from the claimed invention in that it does not teach a method of reducing inflammation due to blepharoconjunctivitis, hay fever, rhinitis, or type 1 hypersensitivity. Neither does the '768 patent teach the use of other anti-inflammatory agents comprising steroids or non-steroids. See Office Action at page 7.

To cure these deficiencies, the Office alleges that the Merck Manual teaches that blepharoconjunctivitis, hay fever, rhinitis, and type 1 hypersensitivity are inflammatory

disorders amenable to treatment by anti-inflammatory agents. Final Office Action at page 7.

Nowhere in the Merck Manual is there any suggestion or motivation to use a toxic protein, let alone a botulinum toxin, in the methods of the claimed invention. The Merck Manual is a general reference having nothing at all to do with the use of protein agents in the treatment of disorders.

Furthermore, nowhere in either of the references of record is there any teaching or suggestion of "*allergic blepharoconjunctivitis*" or "a periocular area" as required by claim 10. For these reasons alone, the rejection of claim 10 should be withdrawn. Neither are there any teachings in any of the references of "hay fever," "allergic forms of eczema," "urticaria," or "inflammatory bowel disease." Should the Office maintain the instant rejection, Applicant respectfully requests that the Office specifically indicate where in the references cited in the rejection these teachings appear.

The Office Action alleges that "one of ordinary skill in the art would have been motivated to make the said substitutions because blepharoconjunctivitis, hay fever, rhinitis, and type 1 hypersensitivity are inflammatory disorders amenable to treatment by anti-inflammatory agents, as taught by the Merck Manual, and steroidal and non-steroidal drugs are common anti-inflammatory agents, also taught by the Merck Manual." Office Action at page 7. Applicants respectfully disagree.

As stated above, the Office Action fails to make a *prima facie* case of obviousness because specific limitations recited in the claims are not taught in the references. The Office has also not indicated where a person having ordinary skill in the art might find a

reasonable expectation of success to arrive at the claimed invention. The Office simply does not address this. The motivation to combine the reference cited in the Office Action is also deficient because there is no suggestion anywhere in the references of using a toxic protein, let alone a botulinum toxin, in the methods of claims 10-12. Applicant respectfully requests that the rejection be withdrawn.

C. The Rejection of Claims 1, 5-8, 10-12, 24-25 and 42-57 under 35 U.S.C. § 112 First Paragraph

Claims 1, 5-8, 10-12, 24-25 and 42-57[2] stand rejected under 35 U.S.C. § 112, first paragraph, because the claims are alleged to lack written description support in the specification.

1. The Law Regarding Written Description

The written description requirement of § 112, ¶ 1 is set forth as follows:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention. 35 U.S.C. § 112, ¶ 1.

The Federal Circuit has interpreted this section as requiring a "written description" of an invention separate from enablement. *Vas-Cath v. Mahurkar*, 935 F.2d

[2] Claims 17-19 and 21-23 are cancelled in the Amendment After Final submitted concurrently herewith.

1555, 1563 (Fed. Cir. 1991) (recognizing the severability of the "written description" and "enablement" provisions of § 112, ¶ 1). Compliance with the written description requirement is essentially a fact-based inquiry that will "necessarily vary depending on the nature of the invention claimed." *Id.* (citing *In re DiLeone*, 58 C.C.P.A. 925, 436 F.2d 1404, 1405, 168 U.S.P.Q. (BNA) 592, 593 (CCPA 1971)).

Federal Circuit precedent clearly establishes that the applicant must convey to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. *Falko-Gunter v. Inglis*, 448 F.3d 1357, 1365 (Fed. Cir. 2006). "The purpose of the written description requirement is to prevent an applicant from later asserting that he invented that which he did not; the applicant for a patent is therefore required 'to recount his invention in such detail that his future claims can be determined to be encompassed within his original creation.'" *Amgen Inc. v. Hoechst Marion Roussel Inc.*, 314 F.3d 1313, 1330, 65 USPQ2d 1385, 1397 (Fed. Cir. 2003) (citing *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1561, 19 USPQ2d 1111, 1115 (Fed. Cir. 1991)).

In the present case, Applicants clearly were in possession of the claimed invention because each of the claims is supported by specific statements in the specification as detailed below.

2. The Specification Provides Adequate Written Description Support for the Pending Claims

Claim 1 recites:

> 1. A method of reducing inflammation, comprising the step of administering a therapeutically effective dose

> of a botulinum toxin to an affected area of a subject suffering from inflammation, wherein the botulinum toxin reduces at least one symptom of inflammation, and wherein said therapeutically effective dose is sufficient to reduce said at least one symptom of inflammation but less than a dose necessary to produce substantial muscle weakness within the affected area.

- Originally filed claim 2 recites "A method of treating inflammation, comprising the step of administering a chemodenervating agent to an anatomic region in a dose just sufficient to reduce inflammation, but below that necessary to cause substantial muscle weakness."
- On page 19 of the specification, Applicant teaches that "Minimum doses range between 0.6 units to 15 units and are far lower than that required to produce regional weakness."
- On page 3 of the specification, in the Summary of the Invention, Applicant teaches that "It has been found that the use of botulinum toxin in doses from 1/3rd to several orders of magnitude less than those associated with treatment of regional movement diseases has been effective to reduce inflammation and adverse sensory experiences associated with the inflammation response."
- On page 4 of the specification, Applicant teaches that "It is a finding of the subject invention that chemodenervative pharmaceuticals such as botulinum toxin in low dosages are effective anti-inflammatory agents.

Typical minimum effective doses range from 0.5-5 units as opposed to 20-600 units used for treatment of movement disorders."

- The limitations of dependent claims 5-8 may be found throughout the specification and, for example, on page 7, lines 13-15; and original claims 5-8.

Withdrawal of the rejection is respectfully requested.

Claim 10 recites:

> 10. A method for treating allergic blepharoconjunctivitis comprising the step of administering a therapeutically effective dose of a botulinum toxin in a periocular area of a subject suffering from blepharoconjunctivitis, thereby reducing inflammation.

- Originally filed claim 10 recites: "A method for treating allergic blepharoconjunctivitis comprising the step of injecting a chemodenervating agent in the periocular area."
- On page 7 of the specification, Applicant teaches that "Although botulinum toxin Type A is the currently preferred chemodenervating agent, other immunotypes of botulinum toxin Type B-G may be substituted based on demonstrated anti-inflammatory efficacy."
- On page 15 of the specification, Applicant teaches "Allergic Blepharoconjunctivitis" and the treatment of four patients with botulinum toxin.

- On page 20 of the specification, Applicant discloses that "The fundamental clinical properties associated with and characterizing inflammation are 1. pain or altered sensation 2. erythema 3. edema 4. heat 5. muscular reactivity (often spasm)."
- Applicant also discloses on page 20 that "In patients having...allergic blepharoconjunctivitis, there has been: 1. Repeated improvement in erythema within the denervation filed 2. Improvement in sensation, pain and or itching within the denervation field 3. Improvement in edema formation within the denervation field 4. Differential in apparent heat release within the denervation field 5. Relaxation of human muscle spasms within the denervation field."
- Results of a treated patient with blepharoconjunctivitis is depicted in Figure 6.
- Results of an animal model of allergic blepharoconjunctivitis is given in Figures 3-5.
- 4 patients receiving beneficial results with allergic blepharoconjunctivitis are described on page 15.

Withdrawal of the rejection is respectfully requested.

Claim 11 recites:

> 11. A method for treating classic type 1 hypersensitivity comprising the step of administrating a botulinum toxin to an affected area of a subject suffering from

classic type 1 hypersensitivity, thereby reducing inflammation.

- Original claim 11 recites "A method for treating classic type 1 hypersensitivity, comprising the step of administering a chemodenervating agent to the affected area."
- On page 5 of the specification, Applicant discloses that "The subject anti-inflammatory agent's unique property relates to suppression of the component for the inflammatory response which occurs rapidly, and which is mediated by neural reflex mechanisms. It has been found that Type 1 hypersensitivity reactions are reduced with the subject anti-inflammatory agent. Such hypersensitivity reactions are classic for rapid expression of the inflammatory response often leading to edema with increased vascular permeability, erythema, abnormal sensory experiences, and increased heat release."
- On page 20 of the specification, Applicant discloses that "The fundamental clinical properties associated with and characterizing inflammation are 1. pain or altered sensation 2. erythema 3. edema 4. heat 5. muscular reactivity (often spasm)."
- Applicant also discloses on page 20 that "In patients having...Type 1 hypersensitivity... there has been: 1. Repeated improvement in erythema within the denervation filed 2. Improvement in sensation, pain and or itching within the denervation field 3. Improvement in edema formation within the denervation field 4. Differential in apparent heat release within

the denervation field 5. Relaxation of human muscle spasms within the denervation field."

- The Guinea pig animal model (page 13, Figures 3-5) is presented as a classic example of type 1 hypersensitivity (IgE mediated with rapid inflammatory responses).

Withdrawal of the rejection is respectfully requested.

Claim 12 recites:

> 12. The method of Claim 11, wherein the hypersensitivity is hay fever, rhinitis, allergic rhinitis, allergic forms of eczema, urticaria, rheumatoid arthritis, inflammatory bowel disease, or asthma.

- Original claim 12 recites "The method of claim 11, wherein the hypersensitivity includes hay fever and rhinitis."
- The Guinea pig animal model used measures allergic hypersensitivity in eye and nasal passages (see Page 13 and Figures 3-5).
- On page 6 of the specification, Applicant discloses that "It will be appreciated that mast cells are known to contain a number of substances important to inflammatory responses in hypersensitivity reactions, and substantially participate in more generalized inflammatory reactions. The mast cell is abundantly found in pathologic tissue specimens in patients with rheumatoid arthritis, inflammatory bowel disease, certain forms of ocular uveitis, eczema, and asthma."

- Page 10 of the specification describes the treatment of a patient with urticaria using botulinum toxin.
- Page 11 of the specification discloses that "Urticaria refers to the formation of hives occurring usually in response to allergic reactions to pollens, foods, dander or other forms of antigens."
- Page 12 of the specification discloses that "Mast cells are closely associated with Type I hypersensitivity reactions."
- Page 12 of the specification discloses that "Mast cells reactivity has been associated with hayfever blepharoconjunctivitis, asthma, allergic rhinitis, and allergic forms of eczema."

Withdrawal of the rejection is respectfully requested.

Claim 24 recites:

> 24. A method for treating inflammation, comprising the step of administering a botulinum toxin to an affected area of a subject suffering from inflammation in a therapeutically effective dose sufficient to reduce a rapid-phase inflammatory response under neural regulation, thereby reducing at least one symptom of inflammation, and wherein said therapeutically effective dose is sufficient to reduce the at least one symptom of inflammation but less than a dose necessary to produce substantial muscle weakness within said affected area.

- On page 7 of the specification, Applicant discloses that "Thus, the subject denervating agent, e.g. botulinum toxin, is demonstrated to achieve a reduction in rapid phase inflammatory responses. The responses are under

neural regulation, involving mast cells degranulating autocoid releases activated by either non-immunologic or immunologic-based processes."

- Originally filed claim 2 recites "A method of treating inflammation, comprising the step of administering a chemodenervating agent to an anatomic region in a dose just sufficient to reduce inflammation, but below that necessary to cause substantial muscle weakness."
- On page 19 of the specification, Applicant teaches that "Minimum doses range between 0.6 units to 15 units and are far lower than that required to produce regional weakness."
- On page 3 of the specification, in the Summary of the Invention, Applicant teaches that "It has been found that the use of botulinum toxin in doses from 1/3rd to several orders of magnitude less than those associated with treatment of regional movement diseases has been effective to reduce inflammation and adverse sensory experiences associated with the inflammation response."
- On page 4 of the specification, Applicant teaches that "It is a finding of the subject invention that chemodenervative pharmaceuticals such as botulinum toxin in low dosages are effective anti-inflammatory agents. Typical minimum effective doses range from 0.5-5 units as opposed to 20-600 units used for treatment of movement disorders."
- Support for dependent claim 25 may be found throughout the specification and, for example on page 7, lines 13-15 and original claim 5.

Withdrawal of the rejection is respectfully requested.

The Office alleges that there is no written description support for "the limitations of new claims 42-57 as further limiting of claims 1, 10, 11 and 24. Applicant respectfully disagrees for the following reasons:

Claim 42 recites:

> 42. The method of claim 10, wherein said therapeutically effective dose is sufficient to reduce at least one symptom of inflammation but less than a dose necessary to produce substantial muscle weakness within said periocular area.

- Originally filed claim 10 recites: "A method for treating allergic blepharoconjunctivitis comprising the step of injecting a chemodenervating agent in the periocular area."
- Originally filed claim 2 recites "A method of treating inflammation, comprising the step of administering a chemodenervating agent to an anatomic region in a dose just sufficient to reduce inflammation, but below that necessary to cause substantial muscle weakness."
- Symptoms of inflammation are cited in the specification on page 20 (pain, erythema, edema, heat). Figures 1-2 depict reduction in edema and erythema. Figures 3-5 depict reduction in edema, erythema and pain in an animal model. Results are discussed on page 14 of the specification.

Withdrawal of the rejection is respectfully requested.

Claim 43 recites:

> 43. The method of claim 11, wherein said therapeutically effective dose is sufficient to reduce at least one symptom of inflammation but less than a dose necessary to produce substantial muscle weakness within said affected area.

- Originally filed claim 2 recites "A method of treating inflammation, comprising the step of administering a chemodenervating agent to an anatomic region in a dose just sufficient to reduce inflammation, but below that necessary to cause substantial muscle weakness."

Withdrawal of the rejection is respectfully requested.

Claim 44 recites:

> 44. The method of claim 10, wherein the chemodenervating agent is selected from the group consisting of botulinum toxins toxin types A, B, C, D, E, F, and G.

- Page 7 of the specification discloses that "Although botulinum toxin Type A is the currently preferred chemodenervating agent, other immunotypes of botulinum toxin Type B-G may be substituted based on demonstrated anti-inflammatory efficacy."

Withdrawal of the rejection is respectfully requested.

Claim 45 recites:

> 45. The method of claim 11, wherein the chemodenervating agent is selected from the group consisting of botulinum toxins toxin types A, B, C, D, E, F, and G.

- Page 7 of the specification discloses that "Although botulinum toxin Type A is the currently preferred chemodenervating agent, other immunotypes of botulinum toxin Type B-G may be substituted based on demonstrated anti-inflammatory efficacy."

Withdrawal of the rejection is respectfully requested.

Claim 46 recites:

> 46. The method of claim 24, wherein said botulinum toxin reduces mast cell degranulation, thereby reducing inflammation.

- Original claim 9 recites "A method for blocking mast cell degranulation, comprising the step of administering a chemodenervating agent to an anatomic region."
- Page 7 of the specification discloses that "the agent works to reduce inflammation by reducing histamine and other preformed mediator releases associated with mast cell degranulation."
- The Guinea pig animal model is useful for measuring mast cell degranulation. Mast cells are abundant in sensitized conjunctiva.

Withdrawal of the rejection is respectfully requested.

Claim 47 recites:

> 47. The method of claim 46, wherein the mast cell is activated by either non-immunologic or immunologic-based processes.

- Page 7 of the specification discloses that "The responses are under neural regulation, involving mast cells degranulating autocoid releases activated by either non-immunologic or immunologic based processes."

Withdrawal of the rejection is respectfully requested.

Claim 48 recites:

> 48. The method of claim 24, wherein the therapeutically effective dose is sufficient to reduce release of preformed mediators of inflammation.

- Page 4 of the specification discloses that "This new bioeffect of anti-inflammatory action is explained by the resultant blockage of mast and nerve cell release of histamine and other preformed mediators which result in vascular dilation, increased permeability, altered sensory experience, edema and erythema. It is thus a finding of this invention that inflammation is inhibited by administration of the subject chemodenervating agent."

Withdrawal of the rejection is respectfully requested.

Claim 49 recites:

> 49. The method of claim 48, wherein the therapeutically effective dose is sufficient to reduce release of leukotrienes, prostaglandins, histamine, serotonin, platelet activating factor, tryptase, or kininogenase.

- Page 7 of the specification discloses that "the agent works to reduce inflammation by reducing histamine and other preformed mediator releases associated with mast cell degranulation."
- Page 6 of the specification discloses that "Mast cell activation has been associated with the production of both preformed mediators such as histamine, newly formed mediators such as leukotrienes and prostaglandins, cytokines, including interleukin-5, interleukin-8, kininogenase, and platelet activating factor."
- Page 11 of the specification discloses that "The process often involves binding of allergens to the IgE receptor of the mast cell membrane bound IgE, causing release of preformed mediators such as histamine and serotonin as well as newly formed mediators from arachadonic acid such as prostaglandins and leukotrienes, platelet activating factor, kinoginase and tryptase, as well as cytokines."

Withdrawal of the rejection is respectfully requested.

Claim 50 recites:

> 50. The method of claim 1, wherein said inflammation is ocular surface allergic inflammation.

- Page 16 of the specification discloses that "It has now been found that the subject agent has useful anti-inflammatory properties capable of blocking ocular surface allergic inflammation in man and animal models, as well as generalized inflammation within the denervation field created."

Withdrawal of the rejection is respectfully requested.

Claim 51 recites:

> 51. The method of claim 24, wherein the therapeutically effective dose is between one third and several orders of magnitude less than the dose necessary to produce substantial muscle weakness in an affected area.

- Page 3 of the specification discloses that "It has been found that the use of botulinum toxin in doses from 1/3rd to several orders of magnitude less than those associated with treatment of regional movement diseases has been effective to reduce inflammation and adverse sensory experiences associated with the inflammatory response."
- Originally filed claim 2 recites "A method of treating inflammation, comprising the step of administering a chemodenervating agent to an anatomic region in a dose just sufficient to reduce inflammation, but below that necessary to cause substantial muscle weakness."

Withdrawal of the rejection is respectfully requested.

Claim 52 recites:

> 52. The method of claim 42, wherein the therapeutically effective dose is between one third and several orders of magnitude less than the dose necessary to produce substantial muscle weakness in an affected area.

- Page 3 of the specification discloses that "It has been found that the use of botulinum toxin in doses from 1/3rd to several orders of magnitude less than those associated with treatment of regional movement diseases has

been effective to reduce inflammation and adverse sensory experiences associated with the inflammatory response."

- Originally filed claim 2 recites "A method of treating inflammation, comprising the step of administering a chemodenervating agent to an anatomic region in a dose just sufficient to reduce inflammation, but below that necessary to cause substantial muscle weakness."

Withdrawal of the rejection is respectfully requested.

Claim 53 recites:

> 53. The method of claim 43, wherein the therapeutically effective dose is between one third and several orders of magnitude less than the dose necessary to produce substantial weakness in an affected area.

- Page 3 of the specification discloses that "It has been found that the use of botulinum toxin in doses from 1/3rd to several orders of magnitude less than those associated with treatment of regional movement diseases has been effective to reduce inflammation and adverse sensory experiences associated with the inflammatory response."
- Originally filed claim 2 recites "A method of treating inflammation, comprising the step of administering a chemodenervating agent to an anatomic region in a dose just sufficient to reduce inflammation, but below that necessary to cause substantial muscle weakness."

Withdrawal of the rejection is respectfully requested.

Claims 54-57 recite:

> 54. The method of claim 1, wherein the at least one symptom of inflammation is heat release, vasodilation, erythema, edema or pain.
>
> 55. The method of claim 54, wherein the at least one symptom of inflammation is pain.
>
> 56. The method of claim 24, wherein the at least one symptom of inflammation is heat release, vasodilation, erythema, edema or pain.
>
> 57. The method of claim 56, wherein the at least one symptom of inflammation is pain.

- Page 20 of the specification discloses that "The fundamental clinical properties associated with and characterizing inflammation are

  1. pain or altered sensation
  2. erythema (redness)
  3. edema
  4. heat
  5. muscular reactivity (often spasm)

  - Page 4 of the specification discloses that "Within this defined area, low dosages of botulinum toxin are demonstrated to block edema, erythema, abnormal sensory experiences, and heat transfer, occurring rapidly over a predefined region."
  - Page 8 of the specification discloses "a photograph of the result after three days of injecting a patient suffering from heat release, vasodilation, erythema, and edema with a chemodenervating agent, showing the protective anti-inflammatory effect of the chemodenervating agent, which effect has been noted in less than 24 hours after injection and prior to the

development of any weakness, indicating novel dose and pharmacological response for the subject anti-inflammatory bioeffect."

Withdrawal of the rejection is requested.

VIII. CLAIMS APPENDIX

Claim 1 (Previously Presented): A method of reducing inflammation, comprising the step of administering a therapeutically effective dose of a botulinum toxin to an affected area of a subject suffering from inflammation, wherein the botulinum toxin reduces at least one symptom of inflammation, and wherein said therapeutically effective dose is sufficient to reduce said at least one symptom of inflammation but less than a dose necessary to produce substantial muscle weakness within the affected area.

Claims 2-4 (Cancelled).

Claim 5 (Previously Presented): The method of Claim 1, wherein the chemodenervating agent is selected from the group consisting of botulinum toxins toxin types A, B, C, D, E, F, and G.

Claim 6 (Previously Presented): The method of Claim 1, wherein the chemodenervating agent is administered in conjunction with another anti-inflammatory agent.

Claim 7 (Original): The method of Claim 6, wherein the other anti-inflammatory agent is a steroid.

Claim 8 (Original): The method of Claim 6, wherein the other agent is non-steroidal.

Claim 9 (Cancelled).

Claim 10 (Previously Presented): A method for treating allergic blepharoconjunctivitis comprising the step of administering a therapeutically effective dose of a botulinum toxin in a periocular area of a subject suffering from blepharoconjunctivitis, thereby reducing inflammation.

Claim 11 (Previously Presented): A method for treating classic type 1 hypersensitivity comprising the step of administrating a botulinum toxin to an affected area of a subject suffering from classic type 1 hypersensitivity, thereby reducing inflammation.

Claim 12 (Previously Presented): The method of Claim 11, wherein the hypersensitivity is hay fever, rhinitis, allergic rhinitis, allergic forms of eczema, urticaria, rheumatoid arthritis, inflammatory bowel disease, or asthma.

Claim 13-23 (Cancelled).

Claim 24 (Previously Presented): A method for treating inflammation, comprising the step of administering a botulinum toxin to an affected area of a subject suffering from inflammation in a therapeutically effective dose sufficient to reduce a rapid-phase inflammatory response under neural regulation, thereby reducing at least one symptom of inflammation, and wherein said therapeutically effective dose is sufficient to reduce the at least one symptom of inflammation but less than a dose necessary to produce substantial muscle weakness within said affected area.

Claim 25 (Previously Presented): The method of Claim 24, wherein the botulinum toxin is selected from the group consisting of botulinum toxin A, B, C, D, E, F and G.

Claims 26-41 (Cancelled).

Claim 42 (Previously Presented): The method of claim 10, wherein said therapeutically effective dose is sufficient to reduce at least one symptom of inflammation but less than a dose necessary to produce substantial muscle weakness within said periocular area.

Claim 43 (Previously Presented): The method of claim 11, wherein said therapeutically effective dose is sufficient to reduce at least one symptom of inflammation but less than a dose necessary to produce substantial muscle weakness within said affected area.

Claim 44 (Previously Presented): The method of claim 10, wherein the chemodenervating agent is selected from the group consisting of botulinum toxins toxin types A, B, C, D, E, F, and G.

Claim 45 (Previously Presented): The method of claim 11, wherein the chemodenervating agent is selected from the group consisting of botulinum toxins toxin types A, B, C, D, E, F, and G.

Claim 46 (Previously Presented): The method of claim 24, wherein said botulinum toxin reduces mast cell degranulation, thereby reducing inflammation.

Claim 47 (Previously Presented): The method of claim 46, wherein the mast cell is activated by either non-immunologic or immunologic-based processes.

Claim 48 (Previously Presented): The method of claim 24, wherein the therapeutically effective dose is sufficient to reduce release of preformed mediators of inflammation.

Claim 49 (Previously Presented): The method of claim 48, wherein the therapeutically effective dose is sufficient to reduce release of leukotrienes, prostaglandins, histamine, serotonin, platelet activating factor, tryptase, or kininogenase.

Claim 50 (Previously Presented): The method of claim 1, wherein said inflammation is ocular surface allergic inflammation.

Claim 51 (Previously Presented): The method of claim 24, wherein the therapeutically effective dose is between one third and several orders of magnitude less than the dose necessary to produce substantial muscle weakness in an affected area.

Claim 52 (Previously Presented): The method of claim 42, wherein the therapeutically effective dose is between one third and several orders of magnitude less than the dose necessary to produce substantial muscle weakness in an affected area.

Claim 53 (Previously Presented): The method of claim 43, wherein the therapeutically effective dose is between one third and several orders of magnitude less than the dose necessary to produce substantial weakness in an affected area.

Claim 54 (Previously Presented): The method of claim 1, wherein the at least one symptom of inflammation is heat release, vasodilation, erythema, edema or pain.

Claim 55 (Previously Presented): The method of claim 54, wherein the at least one symptom of inflammation is pain.

Claim 56 (Previously Presented): The method of claim 24, wherein the at least one symptom of inflammation is heat release, vasodilation, erythema, edema or pain.

Claim 57 (Previously Presented): The method of claim 56, wherein the at least one symptom of inflammation is pain.

IX. EVIDENCE APPENDIX

None.

X. RELATED PROCEEDINGS APPENDIX

None.

Conclusion

Applicants respectfully request reconsideration and withdrawal of the pending rejections and early allowance of the pending claims.

The Commissioner is authorized to charge any additional fees associated with this brief, or credit any overpayment, to Deposit Account No. 13-3250. **EXCEPT** for issue fees payable under 37 C.F.R. § 1.18, the Commissioner is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. §§ 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 13-3250. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with C.F.R. § 1.136(a)(3).

Respectfully submitted,

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